PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Playing board games, cognitive decline and dementia: a French population-based cohort study
AUTHORS	Dartigues, Jean-Francois; Foubert, Alexandra; Le Goff, Mélanie; Viltard, Mélanie; Amieva, Hélène; Orgogozo, Jean; Barberger-Gateau, Pascale; Helmer, Catherine

VERSION 1 - REVIEW

REVIEWER	James A. Mortimer, Ph.D. Professor Department of Epidemiology and Biostatistics University of South Florida No competing interests.
REVIEW RETURNED	11-Apr-2013

THE STUDY	The STROBE checklist is properly filled out and does not contain information that needs to be included in the manuscript.
RESULTS & CONCLUSIONS	This manuscript addresses an important question using data from a large, long-duration, well-conducted longitudinal study. The authors report that non-demented subjects who played board games at baseline are less likely to become demented over the follow-up period. However, when they controlled for baseline MMSE and depression, the association disappeared. (Most of the effect seems to be due to controlling for MMSE, not for depression. The authors should adjust for each separately and the two together in different models to confirm this.) Alternative interpretations are given for this finding, including reverse causation, i.e., people on their way to Alzheimer's are less likely to play board games. If this were the only finding, reverse causation could well explain the results. The authors also use mixed model regression to examine the rate of decline in cognition (MMSE). Because baseline MMSE is "in the model," this analysis adjusts for this parameter in addition to the other covariates. In this model, playing board games was significantly associated with rate of cognitive decline. This finding suggested to the authors that playing board games could slow cognitive decline. It is important to note that the two sets of findings point in opposite directions. In the mixed model regression, the dependent variable is linear rate of cognitive decline. However, as participants approach onset of dementia cognitive decline accelerates as is well documented in the literature including publications from the PAQUID study (non-linear decline). Therefore, the significant finding obtained in the mixed model regression examining only linear decline could be driven by those closer in time to dementia having "steeper" slopes.

	There is a fairly easy way to assess this possibility. The authors could rerun the cognitive decline models, eliminating those who became demented over the entire period or over the first 10 years of follow-up. If the finding remains, then the direction of causation would appear to go from exposure to outcome. If the finding disappears, reverse causation should be considered. Given the very strong association with education of both the exposure and the outcome (dementia) in this cohort, the authors need to use the 5 level education variable in their dataset rather than the dichotomous one used here. It is possible that individuals with higher education (high school, college, etc.) could contribute significantly to the association of interest. The authors might also consider adjusting for APOE, if it turns out to be related to both the exposure and the outcome. The dataset is entirely appropriate for examining the association of interest. However, some additional analyses are needed to clarify the likely directionality of effects.

REVIEWER	Michelle Carlson, Ph.D. Associate Professor Johns Hopkins Bloomberg School of Public Health US
REVIEW RETURNED	29-May-2013

GENERAL COMMENTS	Leisure and social activity was surveyed in 3,777 community-dwelling adults >65 year at baseline in the French Paquid Study and were prospectively followed for incident dementia and depression over 20 years. Over this period, there were 830 incident cases of dementia. In unadjusted models, after 3 years of follow-up, those who played board games at baseline had a 3% risk of dementia vs. 6% in non-players and this risk reduction remained at 10 (16% vs. 27%) and 20 years (47% vs. 58%). Risk reduction remained statistically significant after adjustment for age, education, and other health variables (p=.0.04). The relationship between baseline endorsement of board games and dementia risk became nonsignificant after adjustment for baseline MMSE and depression, suggesting to authors that the association between board games and dementia risk was mediated through the effect of board games on cognition and depression at baseline. This argument for mediation needs to recognize that both MMSE at baseline and follow-ups, and depression were likely used to diagnose dementia. In other words, the association may as likely reflect the explicit use of these measures by clinicians to define the onset of symptoms of dementia. In the Discussion, authors state that playing board games could be a marker of other latent factors or a causal agent in delaying risk for dementia. However, they stop short of explaining whether and why its status as a marker vs. a modifier may matter. Addressing the implications of either role is critical to understanding the significance of this paper and to future directions. Specific Questions and Edits:

	Methods: p. 6- A potential limitation that should be addressed is the weekly time scale used in the Activity questionnaire, asking whether a given activity was participated in “at least once a week.” It is reasonable to expect that some of the activities surveyed may be endorsed once every 2 or 4 weeks, thus restricting their endorsement. p. 7- please correctly refer to the “S” in the MMSE, as “State” and not “Status.”

VERSION 1 – AUTHOR RESPONSE

Reviewer: James A. Mortimer, Ph.D.
Professor
Department of Epidemiology and Biostatistics
University of South Florida
Tampa, FL 33612

No competing interests.

The STROBE checklist is properly filled out and does not contain information that needs to be included in the manuscript.

This manuscript addresses an important question using data from a large, long-duration, well-conducted longitudinal study. The authors report that non-demented subjects who played board games at baseline are less likely to become demented over the follow-up period. However, when they controlled for baseline MMSE and depression, the association disappeared. (Most of the effect seems to be due to controlling for MMSE, not for depression. The authors should adjust for each separately and the two together in different models to confirm this.)

Response: As recommended by the reviewer, separate adjustments were made on MMSE (Table 3) and depression (Table 4). In both analyses, the significant relationship between board game playing (BGP) and dementia disappeared. But as postulated by the reviewer most of the effect seems to be due to controlling for MMSE:

Table 3: Risk of dementia according to board game playing in the Paquid Cohort. Multivariate Cox model with adjustment on age, gender, education, marital status, history of stroke, diabetes and MMSE score

HR 95%CI p Value
Board game 0.94 0.80-1.09 0.41
(players vs non-players)
MMSE score 0.91 0.88-0.93 <.0001

Table 4: Risk of dementia according to board game playing in the Paquid Cohort. Multivariate Cox model with adjustment on age, gender, education, marital status, history of stroke, diabetes and depression

HR 95%CI Value
Board game 0.89 0.76-1.03 0.12
(players vs non-players)
Depression (yes vs no) 1.48 1.25-1.77 <.0001

Alternative interpretations are given for this finding, including reverse causation, i.e., people on their way to Alzheimer's are less likely to play board games. If this were the only finding, reverse causation could well explain the results.

The authors also use mixed model regression to examine the rate of decline in cognition (MMSE). Because baseline MMSE is "in the model," this analysis adjusts for this parameter in addition to the other covariates. In this model, playing board games was significantly associated with rate of cognitive decline. This finding suggested to the authors that playing board games could slow cognitive decline.

It is important to note that the two sets of findings point in opposite directions. In the mixed model regression, the dependent variable is linear rate of cognitive decline. However, as participants approach onset of dementia cognitive decline accelerates as is well documented in the literature including publications from the PAQUID study (non-linear decline). Therefore, the significant finding obtained in the mixed model regression examining only linear decline could be driven by those closer in time to dementia having "steeper" slopes.

There is a fairly easy way to assess this possibility. The authors could rerun the cognitive decline models, eliminating those who became demented over the entire period or over the first 10 years of follow-up. If the finding remains, then the direction of causation would appear to go from exposure to outcome. If the finding disappears, reverse causation should be considered.

Response : As recommended by the reviewer, we have rerun the cognitive decline model eliminating subjects who became demented over the entire period (Table 5) or over the first ten years of FU (Table 6). The beta coefficients slightly decrease (from 0.01 to 0.008) but become non significant (respectively p=0.07 and p=0.15). However a decrease of statistical power and a selection of the sample could explain these results. At the whole, this supplementary analysis is more in favour of a reverse causation from outcome to exposure as postulated by the reviewer. These analyses were added to the paper in the results section and in the discussion section (page 10 and page 13).

Table 5: Mixed model regression to study the relationship between board game playing and cognitive decline represented by MMSE score. The subjects who became demented over the entire period were eliminating. (n=2137)

Solution for fixed effects
Beta coefficient p-value
Board game playing(BGP) 0.15 0.001
Time*BGP 0.008 0.07
Education (higher vs lower) 0.90 <.0001
Time*education -0.001 0.84
Gender (female vs male) 0.02 0.67
Time*gender -0.01 0.001
Age at baseline -0.05 <.0001
Time*age -0.001 0.0005
History of stroke (yes vs no) -0.10 0.24
Diabetes (yes vs no) -0.12 0.07

Table 6 Mixed model regression to study the relationship between board game playing and cognitive

decline. The subjects who became demented over the first ten years of FU were eliminating. (n=2531)

Solution for fixed effects
Beta coefficient p-value
Board game playing 0.17 <.0001
Time*BGP 0.007 0.15
Education (higher vs lower) 0.88 <.0001
Time*education 0.003 0.55
Gender (female vs male) 0.06 0.13
Time*gender -0.02 <.0001
Age at baseline -0.05 <.0001
Time*age -0.001 0.01
History of stroke (yes vs no) -0.14 0.10
Diabetes (yes vs no) -0.14 0.02

Given the very strong association with education of both the exposure and the outcome (dementia) in this cohort, the authors need to use the 5 level education variable in their dataset rather than the dichotomous one used here. It is possible that individuals with higher education (high school, college, etc.) could contribute significantly to the association of interest.

Response : As recommended by the reviewer, we have reanalysed the data with a five level education variable. The results remain exactly the same for the relation between playing board game and dementia (HR=0.86, p=0.046). This five level variable replaced the dichotomous variable in the paper (pages 7,9 and 11).

The authors might also consider adjusting for APOE, if it turns out to be related to both the exposure and the outcome.

Response : The adjustment on APOE 4 genotype is only possible on a subsample of the Paquid cohort of 618 subjects. The proportion of APOE 4 carriers is the same according to board game playing (23.4% vs 21.2%, p=0.5). Thus the risk of confounding effect is weak. In the subsample of subjects with APOE genotype, after adjustment on APOE 4 genotype, the HR for dementia related to playing board game decreased to 0.74 but was no more significant (p=0.06) (Table 7). This analysis was added in the results section (page 7,8,9,10 and 13).

Table 7: Risk of dementia according to board game playing in the Paquid Cohort. Multivariate Cox model with adjustment on age, gender, education, marital status, history of stroke, diabetes and APoE4 genotype.

HR 95%CI p Value
Board game 0.74 0.53-1.02 0.06
(players vs non-players)
ApoE4 carriers vs no 2.01 1.44-2.80 <.0001

The dataset is entirely appropriate for examining the association of interest. However, some additional analyses are needed to clarify the likely directionality of effects.

Reviewer: Michelle Carlson, Ph.D.
Associate Professor
Johns Hopkins Bloomberg School of Public Health

US

Leisure and social activity was surveyed in 3,777 community-dwelling adults >65 year at baseline in the French Paquid Study and were prospectively followed for incident dementia and depression over 20 years. Over this period, there were 830 incident cases of dementia. In unadjusted models, after 3 years of follow-up, those who played board games at baseline had a 3% risk of dementia vs. 6% in non-players and this risk reduction remained at 10 (16% vs. 27%) and 20 years (47% vs. 58%). Risk reduction remained statistically significant after adjustment for age, education, and other health variables (p=.0.04).

The relationship between baseline endorsement of board games and dementia risk became nonsignificant after adjustment for baseline MMSE and depression, suggesting to authors that the association between board games and dementia risk was mediated through the effect of board games on cognition and depression at baseline. This argument for mediation needs to recognize that both MMSE at baseline and follow-ups, and depression were likely used to diagnose dementia. In other words, the association may as likely reflect the explicit use of these measures by clinicians to define the onset of symptoms of dementia.

Response: We agree with this comments and we have added a sentence underlying this point in the discussion section (page 13).

In the Discussion, authors state that playing board games could be a marker of other latent factors or a causal agent in delaying risk for dementia. However, they stop short of explaining whether and why its status as a marker vs. a modifier may matter. Addressing the implications of either role is critical to understanding the significance of this paper and to future directions.

Response: Effectively, we have to develop this explanation and its implications for the significance of the paper and future direction. We propose to add sentences to the discussion section to develop the implications and future directions (page 13).

Specific Questions and Edits:
Methods:
p. 6- A potential limitation that should be addressed is the weekly time scale used in the Activity questionnaire, asking whether a given activity was participated in “at least once a week.” It is reasonable to expect that some of the activities surveyed may be endorsed once every 2 or 4 weeks, thus restricting their endorsement.

Response: We agree with this comment and have added this limit of the paper in the discussion section (page 14).

p. 7- please correctly refer to the “S” in the MMSE, as “State” and not “Status.”
Response: Made (page 7)

VERSION 2 – REVIEW

REVIEWER	James A. Mortimer, Ph.D. Professor University of South Florida USA no competing interests
REVIEW RETURNED	23-Jul-2013

THE STUDY	The authors conclude that there is possible beneficial effect of board game playing on the risk of dementia and that this is mediated by less cognitive decline and less depression in elderly board players. However, the most valid results are those shown in Model 2 ot Table 2 , where board game playing is associated with an HR of 0.96 (p=0.62) when baseline MMSE score and depression are added as covariates. A second mixed model analysis eliminating those who became demented showed smaller beta coefficients, which were also non-significant. It is important to recognize that those remaining after elimination of the incident demented persons include many who are likely to develop dementia in the future. Non-demented participants in the cohort at the time of completion of the current data collection may be the verge of becoming demented or certainly within 10 years of this outcome. Therefore, propensity to becoming demented could offer an explanation for the non-significant trends found.
RESULTS & CONCLUSIONS	The results do answer the research question regarding whether those playing board games have lower risk of dementia, and the answer appears to be that the lower risk is attributable to confounding by baseline MMSE and depression. This appears to be a different conclusion from that reached by the authors. The analyses of rate of decline by board games may well be related to pre-clinical cognitive decline related to risk of dementia. This manuscript is important in that it is based on longer follow-up. What is needed is a more cautious interpretation of the findings, acknowledging the fact that the effects reported could be based on cognitive loss at the time of baseline assessment in those who were becoming demented.

VERSION 2 – AUTHOR RESPONSE

Reviewer: James A. Mortimer, Ph.D.
Professor
University of South Florida
USA

no competing interests

The authors conclude that there is possible beneficial effect of board game playing on the risk of dementia and that this is mediated by less cognitive decline and less depression in elderly board players. However, the most valid results are those shown in Model 2 ot Table 2 , where board game playing is associated with an HR of 0.96 (p=0.62) when baseline MMSE score and depression are added as covariates.

A second mixed model analysis eliminating those who became demented showed smaller beta coefficients, which were also non-significant. It is important to recognize that those remaining after elimination of the incident demented persons include many who are likely to develop dementia in the future. Non-demented participants in the cohort at the time of completion of the current data collection may be the verge of becoming demented or certainly within 10 years of this outcome. Therefore, propensity to becoming demented could offer an explanation for the non-significant trends found.

The results do answer the research question regarding whether those playing board games have lower risk of dementia, and the answer appears to be that the lower risk is attributable to confounding by baseline MMSE and depression. This appears to be a different conclusion from that reached by the authors.

The analyses of rate of decline by board games may well be related to pre-clinical cognitive decline related to risk of dementia.

This manuscript is important in that it is based on longer follow-up.

What is needed is a more cautious interpretation of the findings, acknowledging the fact that the effects reported could be based on cognitive loss at the time of baseline assessment in those who were becoming demented.

We agree with the comment and we are willing to change our conclusion. (page 13)